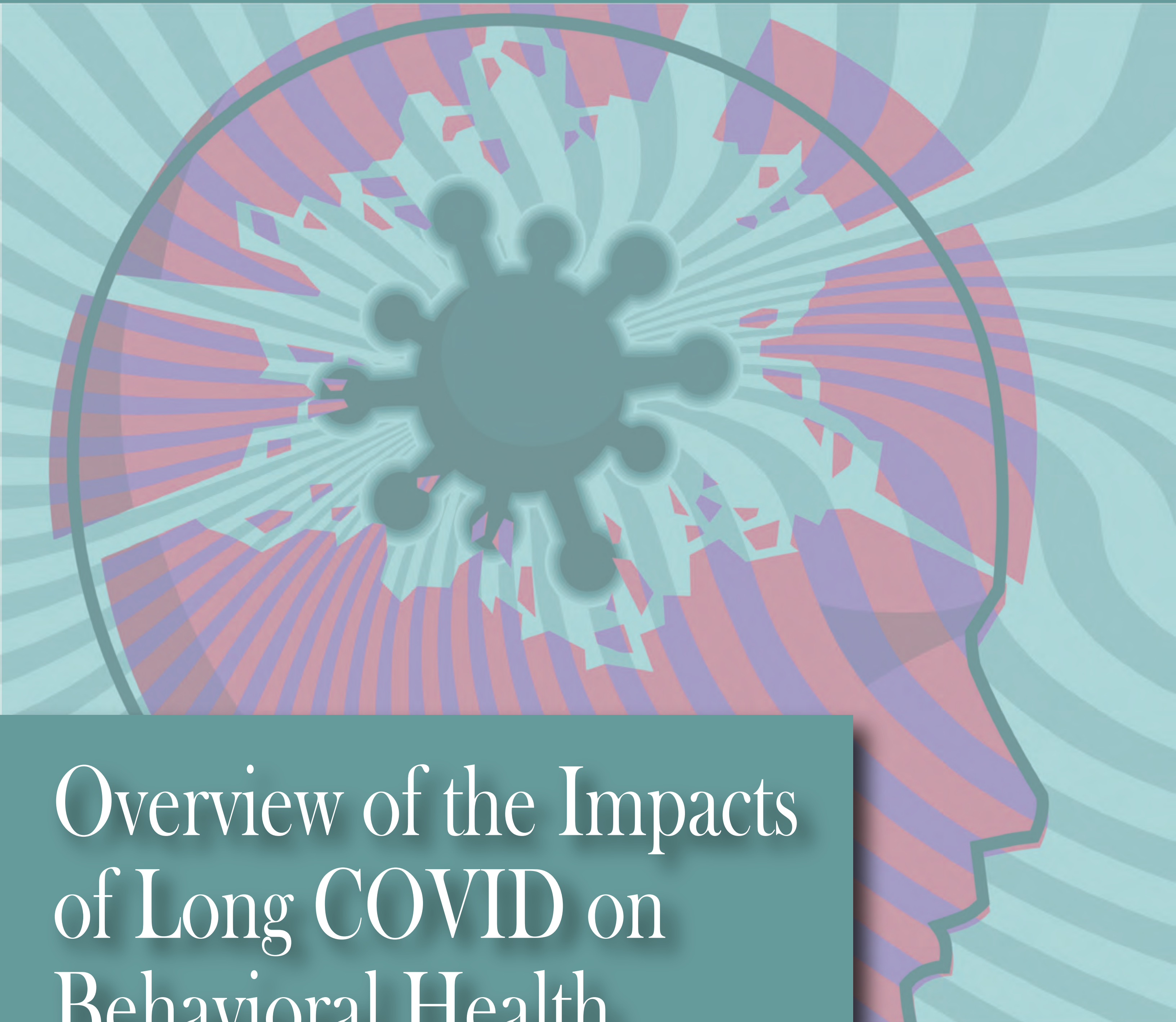

Overview of the Impacts of Long COVID on Behavioral Health

SAMHSA
Substance Abuse and Mental Health Services Administration

Overview of the Impacts of Long COVID on Behavioral Health

Acknowledgments

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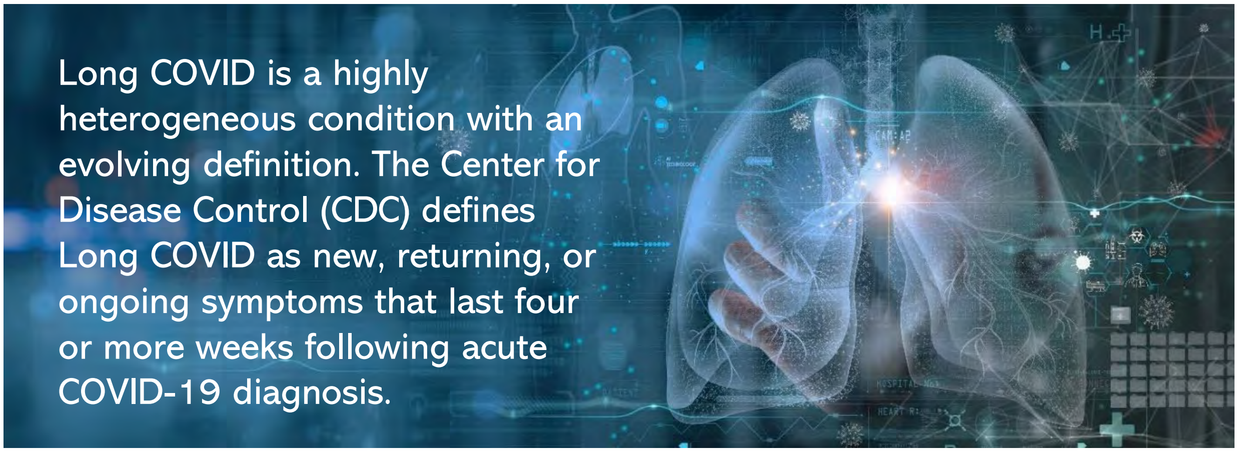
Post-Acute Sequelae of COVID-19 (PASC) or "Long COVID"

The coronavirus disease-2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has profoundly impacted individual health and well-being globally. As of May 2022, there were a total of 81,717,488 reported cases and over one million COVID-19-related deaths in the United States alone.[1] While the effects of COVID-19 vary widely, from asymptomatic or mild disease to multi-organ failure and death, most people make a full recovery from the virus. Unfortunately, however, a substantial proportion of survivors continue to report persistent symptoms often referred to as post-acute sequelae of COVID-19 (PASC) in the literature or "Long COVID", presenting a significant and ongoing public health crisis.[2]



Long COVID is a highly heterogeneous condition with an evolving definition. Centers for Disease Control (CDC) also refers to this as Post-COVID-19 Conditions (PCC) and defines Long COVID as new, returning, or ongoing symptoms that last four or more weeks following acute COVID-19 diagnosis, whereas the World Health Organization (WHO) guidelines suggest it must be present three months from onset of SARS-CoV-2 infection, persist for at least two months, and cannot be explained by an alternative diagnosis.[3,4,5] The condition encompasses an array of approximately 200 different symptoms that are often variable, wide-ranging, and may relate to multiple organ systems, including respiratory, cardiovascular, musculoskeletal, gastrointestinal, neurological, psychological/psychiatric, and dermatologic. The non-specific nature of symptoms and the lack of a consensus definition have made diagnostic efforts challenging, and there is great variability in the course, prognosis, and outcomes as well as who is at greatest risk of developing Long COVID.

The condition encompasses an array of approximately 200 different symptoms that are often variable, wide-ranging, and may relate to multiple organ systems, including respiratory, cardiovascular, musculoskeletal, gastrointestinal, neurological, psychological/psychiatric, and/or dermatologic.

The estimated number of Long COVID patients in the United States is substantial, with several studies approximating that at least 30% of COVID-19 survivors develop long-term sequelae.[6,7]

According to the U.S. Government Accountability Office, this estimate likely translates to between 7.7 to 23 million people living with Long COVID in the United States alone.[8] The most recent literature suggests that Long COVID may be more likely to occur in younger adults (<55 years) and can follow both non-severe (i.e., mild, or asymptomatic) or severe acute COVID-19. A recent analysis of 78,252 health insurance claims in the United States found that two-thirds of patients with Long COVID were between the ages of 36 and 64, and nearly 11% were younger than age

22.[9] Further, at least one-third of the sample did not have any pre-existing health conditions.[10] Importantly, however, this study only captured a privately insured population and thus, does not reflect the scope and burden of Long COVID in older adults and low-income communities.

Cognitive and Psychiatric Symptoms Associated with Long COVID

Post-COVID-19 cognitive impairment and psychiatric morbidity have complex, and likely bidirectional relationships. It is well known that mental health disorders (e.g., depression) can contribute to cognitive impairment,[17] and likewise that impaired cognition can contribute to poor functional outcomes, which may precipitate or exacerbate mental health problems. **Adding to this already complex relationship are other pandemic-related factors, such as social isolation, loneliness, financial and occupational instability, bereavement, and systemic health and social inequities, among other psychosocial stressors.[18] Together, these factors may contribute to and have a differential impact on individuals with Long COVID.**

In comparison to those not infected, COVID-19 survivors show increased rates of mental health and cognitive problems.[19,20]

A meta-analysis of studies around the world showed that the overall prevalence of depression, anxiety, and sleep disturbances among COVID-19 survivors was 45%, 47%, and 34%, respectively. Whereas, those levels were 33%, 31%, and 20%, respectively, in the general non-COVID population during the pandemic.[21] A systematic review also found indications of cognitive impairment and at least one psychiatric disorder six months post-COVID-19 in approximately 56% of patients, with difficulty concentrating (24%) and generalized anxiety disorder (30%) being among the most prevalent Long COVID sequelae.[22] Likewise, a study of 236,379 adults with Long COVID demonstrated that the estimated incidence of a neurologic or psychiatric diagnosis after six months was approximately 34%, with approximately 13% receiving their first ever psychiatric diagnosis.[23] While these rates were highest for those hospitalized (39%) or critically ill (46%), the incidence and relative risk of neurologic and psychiatric diagnoses were also increased by 32% in those with non-severe COVID-19 compared with a matched cohort of patients with other health conditions (e.g., influenza) occurring contemporaneously during the COVID-19 pandemic.[24]

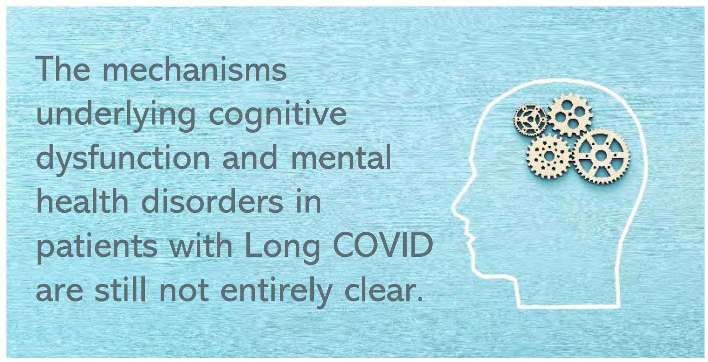
Indeed, while patients with non-severe COVID-19 are also at risk for Long COVID,[25] **accumulating evidence suggests that cognitive and psychiatric sequelae are more pronounced in individuals who were hospitalized or treated in intensive care settings for COVID-19.** For example, in a relatively young cohort of 740 patients (mean age 49) who had mild, moderate, or severe COVID-19, cognitive impairment in at least one domain was prevalent in 25% of the sample approximately eight months later.[26] However, the frequency and severity of impairment was greatest among patients who had been hospitalized for severe disease (up to 39%).[27] Similarly, another study of 382 patients found that anxiety and depression occurred in over 90% of patients six months after hospitalization for COVID-19.[28] While recent studies have found that vaccination for COVID-19 may at least partially

reduce risk for Long COVID,[29] vaccination also helps prevent severe COVID-19, which may account for the reduction in Long COVID risk to a degree.

Many individuals with Long COVID have had to adjust to an entirely new way of life.

Many individuals with Long COVID have had to adjust to an entirely new way of life, either due to acquired physical or cognitive disability, or due to the social and occupational consequences of those limitations. **The impact on individual functioning varies greatly**; many individuals have become unable to continue their normal daily routines, while others find that they can still somewhat manage their responsibilities, but with significantly greater effort. Both scenarios can present substantial cognitive and mental health challenges, leaving patients with Long COVID feeling fatigued, unable to take pleasure from activities they once enjoyed, and feeling anxious and fearful of whether they will be able to return to their baseline level of functioning. Altogether, the multifactorial nature of Long COVID has been a challenge to understand, leaving researchers with more questions than answers regarding the biological, psychological, and sociological underpinnings of Long COVID cognitive and psychiatric sequelae.

Potential Mechanisms



The mechanisms underlying cognitive dysfunction and mental health disorders in patients with Long COVID are still not entirely clear. Several hypotheses have been formulated to explain the impact of SARS-CoV-2 on the central nervous system (CNS), including direct (e.g., viral invasion) and indirect (e.g., inflammation, hypoxia, vascular dysfunction) causes. In line with the behavior of prior coronaviruses and based on evidence from clinical, pathological, and molecular studies,[30] it is possible that the virus may invade the brain via the olfactory nerve, which is responsible for sense of smell, thereby inducing CNS damage and neuroinflammation. However, this hypothesis remains controversial as most of the evidence has been from autopsy studies. Other investigations have failed to find viral proteins in cerebrospinal fluid of survivors.[31]

A more likely explanation is that of systemic immune dysfunction, including neuroinflammation and autoimmune dysregulation, which can cause damage to the brain.[32,33] Indeed, studies examining blood and cerebrospinal fluid in COVID-19 survivors have found elevated inflammatory markers, characteristic of an aberrant neuroimmune response or "cytokine storm" in both severe and non-severe cases.[34-36] This cytokine cascade can trigger vascular inflammation and cause vascular dysfunction,[37] including thrombosis and microangiopathy (microscopic blood clots), which can lead to neurologic symptoms and stroke.[38] These proposed mechanisms are generally consistent with Long COVID cognitive and psychiatric sequelae, as inflammation is a well-known risk factor for cognitive impairment and psychological morbidity,[39] even months after the initial illness.[40] A recent study in COVID-19 survivors demonstrated that systemic inflammation following hospital discharge was able to predict both cognitive dysfunction and depression severity at three-months follow-up.[41] In addition, cerebrovascular disease and stroke have also been associated with cognitive impairment and depression.[42]

A more likely explanation is that of systemic immune dysfunction, including neuroinflammation and autoimmune dysregulation, which can cause damage to the brain.

Part of the challenge with understanding the pathophysiology of Long COVID is the diverse clinical presentations of acute COVID-19.

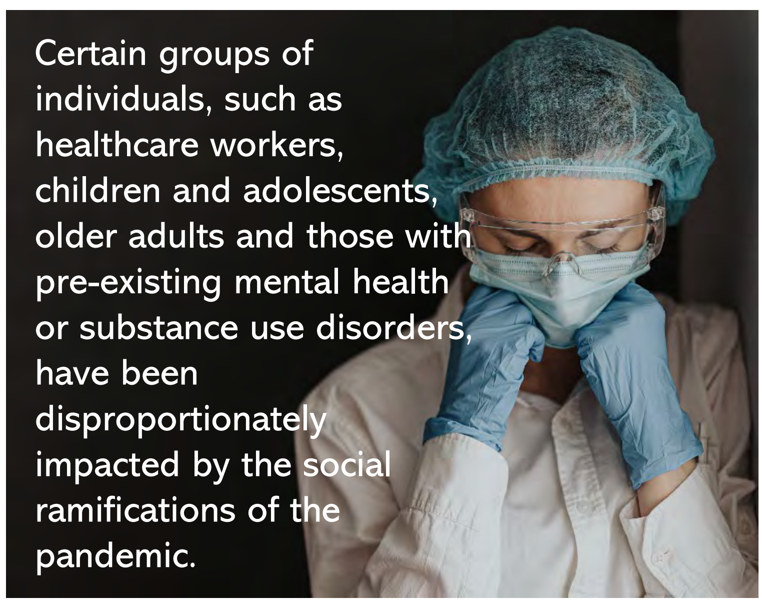
The majority of COVID-19 survivors have mild/asymptomatic or moderate acute disease. In these cases, inflammatory (i.e., cytokine storm) or vascular mechanisms appear to be the predominant CNS complication. For critically ill survivors, the impact to the CNS may be multifactorial and also include hypoxia, hospitalization-related factors (e.g., sedatives, steroid medications, being on a ventilator, delirium), and other systemic and metabolic disturbances.[43] This is consistent with the well-known literature on post-intensive care syndrome (PICS).[44]

Recent neuroimaging studies have begun to shed light on the potential for SARS-CoV-2 to injure the brain (i.e., directly or indirectly) and contribute to cognitive and psychiatric sequelae. A recent UK Biobank study[45] with pre- and post-infection brain scans of 401 mild SARS-CoV-2 cases and 384 non-infected controls found that, in comparison to controls, SARS-CoV-2 cases had greater tissue damage in regions connected to the olfactory cortex (linked to sense of smell), greater reduction in overall brain volume, and greater cognitive decline.[46] Other neuroimaging studies have similarly demonstrated widespread disruption of microstructural brain integrity as well as hypometabolism in frontoparietal and medial temporal areas post-COVID-19, regions that are highly implicated in cognitive processes and mental health disorders.[47-49] Such studies are critical for our understanding of Long COVID symptoms, as it helps us make sense of brain-related changes that could help explain post-COVID cognitive and psychiatric symptoms.

SARS-CoV-2 Infection and the Global Pandemic Environment

In addition to the mental health challenges that may contribute to Long COVID, other social factors inherent to the global pandemic have made it challenging to determine whether those infected by SARS-CoV-2 differ from those merely affected by the global pandemic. In addition to examining biological mechanisms, one must consider the context or environment in which the condition exists. Long COVID came into existence against the backdrop of a global pandemic with tremendous social and political changes. With the rapid spread of SARS-CoV-2 arose the strict implementation of widespread social restrictions (e.g., quarantine, social distancing measures), which initiated and exacerbated behavioral and cognitive symptoms in a substantial proportion of the population.

In an effort to protect the groups most vulnerable to morbidity and mortality from COVID-19, social restrictions during the pandemic also resulted in loss of important resources, including unemployment, adequate healthcare access, and for many, companionship and social support. In the first year of the pandemic alone, the WHO reported that there was a 25% increase in anxiety and depression in the general population. Social isolation from quarantine measures was associated with increased depression, anxiety, and loneliness,[50] which persisted over time. Even two years later, while the lifting of social restrictions has somewhat improved the situation, nationwide surveys have shown that loneliness, fear of infection, survivor's guilt, financial worries, bereavement, and "pandemic fatigue" have perpetuated mental health problems.[51]



Certain groups of individuals, such as healthcare workers, children and adolescents, older adults and those with pre-existing mental health or substance use disorders, have been disproportionately impacted by the social ramifications of the pandemic. Frontline healthcare workers, for example, have had to manage an exceptional number of challenges in the delivery of quality care, working extremely long hours under high pressure, all while fearing infection and facing moral dilemmas relating to lack of equipment, low staffing, and ambiguous treatment guidelines early in

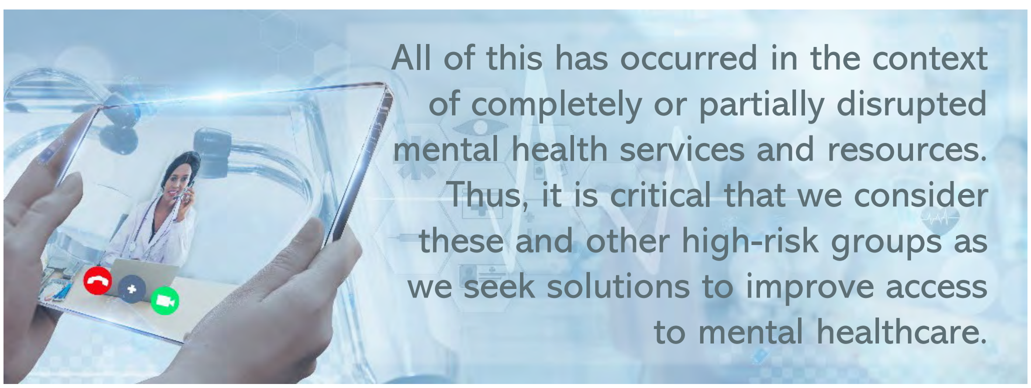
the pandemic. As a result, one study showed that, regardless of COVID-19 status, 53% of healthcare workers reported symptoms of at least one mental health condition, including depression (32%), anxiety (30%), PTSD (37%), and suicidal ideation (8%).[52,53]

Parents of young children have experienced significantly greater stress and mental health burden than those without young children.[54] Similarly, children between the ages of 5 and 7 have reported heightened stress and feeling nervous or anxious since the beginning of the pandemic.[55] Children and adolescents have faced disruptions in their daily routines, learning and socialization, together with loss of loved ones.[56] Likely a result of this high stress environment, many children have also faced increased adversity at home, including greater risk of domestic violence and maltreatment.[57]

Older adults have a higher risk of infection and mortality from COVID-19, and as such, social isolation has become a necessary problem for this population. The effect of loneliness on older adults has been a topic of particular concern, as it has been associated with increased risk of hospitalization.[58] One study found that approximately 40% of adults over age 60 reported loneliness during the pandemic, which led to increased risk of mental health problems.[59] Conversely, another study found that a recent diagnosis of a mental health disorder predicted increased risk for COVID-19 infection and adverse COVID-19 outcomes.[60]

Those with pre-existing mental health or substance use disorders are also at high risk for poor mental, cognitive, and physical health outcomes.

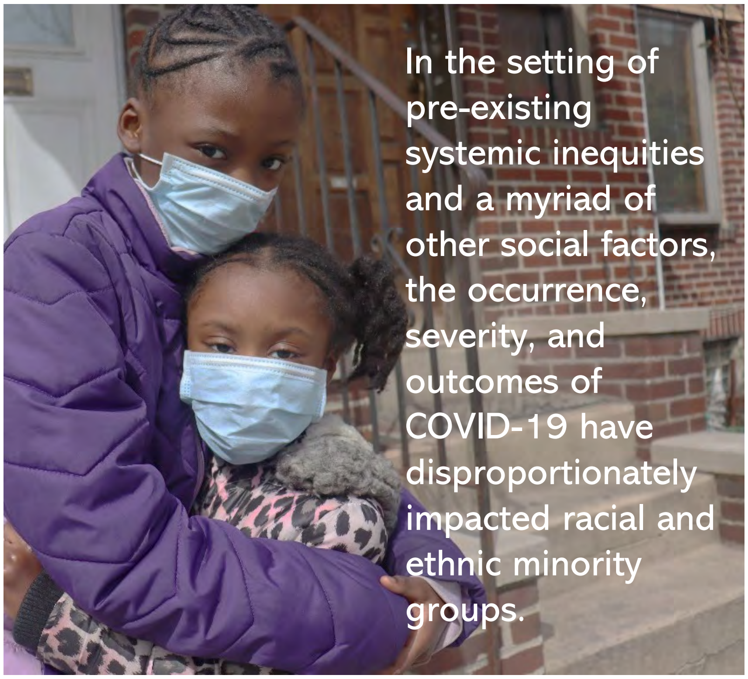
Individuals with a prior psychiatric history showed significantly higher scores on scales for general psychological disturbance, posttraumatic stress disorder (PTSD), and depression.[61] Those with psychosis have been observed to have greater risk of death from COVID-19.[62] Increases in substance use and drug overdoses in the United States have steadily accelerated since March 2020, with approximately 13% of United States adults reporting they had either started or increased use of illicit substances to cope with stress or emotions related to COVID-19.[63,64] Further, the pandemic continues to present unique challenges for people in substance use recovery, with disruption in treatment availability and limited access to support groups.[65] All of this has occurred in the context of completely or partially disrupted mental health services and resources.[66] Thus, it is critical that we consider these and other high-risk groups as we seek solutions to improve access to mental healthcare.



Widening of Health Disparity Gaps

The COVID-19 pandemic initially unfolded amidst protests, calling for increased racial equity for Black populations, as well as an increase in discrimination and hate crimes of Asian individuals.[67] In the setting of pre-existing systemic inequities and a myriad of other social factors, the occurrence, severity, and outcomes of COVID-19 have disproportionately impacted racial and ethnic minority groups. Indeed, overall age-adjusted COVID-19-related deaths in the United States have been highest among non-Latinx Black and non-Latinx American Indian/Alaskan Native populations. The prevalence of COVID-19 cases and hospitalizations have also been greatest among Black and

Latinx communities nationwide.[68] While the causes of COVID-19 health inequities are multifactorial, social determinants of health are likely most responsible.



The model of allostatic load and oxidative stress provides a clear link between psychosocial stressors and chronic health conditions, leading to reduced immunity, inflammation, and consequently, to negative health outcomes.[69] This model suggests that experiences with discrimination and racism are powerful determinants of health and mental health.[70] In addition, differences in environmental exposure, differential access to testing and treatment, social disadvantages (e.g., socioeconomic status, unemployment, inadequate health insurance), and susceptibility from common pre-existing comorbid health conditions, have all served to continually widen health disparity gaps.[71] As a result, the mental health ramifications of COVID-19 inequities have been substantial. Rates of depression have increased during the pandemic across all racial and ethnic groups. Black, Latinx, and Asian children, who are twice as likely as non-Latinx white children to live with a grandparent or older caregiver, have had higher rates of bereavement during the pandemic, as well as a greater risk of orphanhood due to COVID-19-related deaths of grandparents or caregivers.[72] Further, access to appropriate mental health care has been a significant barrier for racial and ethnic minority populations, with one study reporting that only 31% of Black participants received mental health treatment, compared with 48% of White participants.[73]

This model suggests that experiences with discrimination and racism are powerful determinants of health and mental health.

The higher prevalence and severity of COVID-19 in racial and ethnic minority groups, in the setting of pre-existing social and economic inequities, suggests that this population may also be differentially impacted by the chronicity of Long COVID.

As such, particular attention should be paid to providing equitable access to treatment and other resources (e.g., access to specialized post-COVID-19 clinics, rehabilitation), increasing inclusion of racial and ethnic minoritized groups in clinical trials and other research, and spreading awareness about Long COVID through community outreach and engagement groups.

Potential Long-Term Implications

Given the known implications of cognitive and psychiatric symptoms included in the global burden of disability, it seems particularly appropriate to project how the effects of Long COVID on the CNS will continue to contribute to chronic disease burden in the coming years. While anecdotal reports of symptom improvement have recently begun to emerge, there is also evidence that a subset of patients with Long COVID may endure persistent, long-term (i.e., at least 1 year after acute COVID-19 diagnosis) neurologic and psychiatric disorders.[74] Some risk factors for long-term sequelae have been proposed, including severity of acute COVID-19, cerebrovascular events (e.g., strokes) and

chronically elevated inflammatory markers. However, adequate characterization of the longitudinal trajectory of post-COVID-19 cognitive and psychiatric sequelae and associated risk factors is still needed.

Extrapolating from other research areas, it is possible that COVID-19 may confer an increased risk for developing neurodegenerative diseases.[75-77] Multiple lines of evidence suggest that certain viral infections may increase risk for neurodegenerative and neurobehavioral conditions.[78] Prior to the pandemic, this had been extensively studied in common viral infections such as Epstein-Barr virus (EBV) and herpes simplex virus 1 (HSV1), which have been associated with molecular processes in cognitive decline, Alzheimer's, and Parkinson's disease.[79,80] It is suspected that neuroinflammation may occur as a result of these viruses, which accompanies the most common neurodegenerative disorders. Similarly, the cytokine storm and neuroinflammation resulting from COVID-19 is likely a key contributor to the neurologic and psychiatric sequelae of COVID-19.

Indeed, inflammation is a known risk factor for cognitive impairment and neurodegenerative disease, and there are several inflammatory markers implicated in this relationship, including interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α).[81,82] These and other inflammatory markers have been found to be elevated in patients with Long COVID,[83,84] suggesting they may be associated with long-term sequelae. Acute COVID-19 is also associated with heightened risk of stroke, which has been independently associated with cognitive decline and dementia.[85] Similarly, olfactory dysfunction, or dysfunction in sense of smell, which is commonly reported by COVID-19 survivors,[86] may also confer long-term cognitive impairment risk. In other conditions (e.g., mild cognitive impairment, Alzheimer's disease), olfactory dysfunction has been considered a marker for cognitive impairment and neurodegeneration.[87,88]

Survivors of severe COVID-19 who required hospitalization or intensive care are likely at particular risk for poor long-term outcomes, just as other critical illnesses have consistently posed challenges for survivors.[89] It is well-known that patients with acute respiratory distress syndrome (ARDS) can experience a high prevalence of cognitive impairment,[90] with approximately 45% exhibiting long-term deficits, even after 5-years.[91,92] Similar data exist for 30-80% of patients treated in the intensive care unit for any etiology, known as PICS, which can result in a constellation of long-term cognitive, psychiatric, and/or physical disability.[93] While cognitive and psychiatric sequelae can improve over time for a subset of individuals,[94] extrapolating from other illnesses, a substantial proportion may remain with long-term chronic sequelae.[95]

Drawing parallels from prior human coronaviruses also provides insight into the potential long-term implications of SARS-CoV-2 infection. Following the SARS-CoV-1 pandemic of 2002 and MERS-CoV in 2012, a systematic review found that approximately 19% of survivors had memory impairment and 33% had executive dysfunction post-illness.[96] A follow-up study of SARS-CoV-1 survivors also found that four years later, psychiatric morbidities and chronic fatigue continued to be clinically significant, including PTSD (55%), depression (39%), panic disorder (33%), and obsessive compulsive disorder (15.6%).[97] Additionally, the emergence of mental health disorders in middle to late life has been associated with poor long-term health outcomes, including cognitive decline, dementia, and increased risk of mortality.[98]

Taken together, these data strongly support an expected increase in cognitive and psychiatric sequelae of COVID-19 infection in the coming years, including cognitive decline, dementia, and affective disorders, among others.[99] From a health systems viewpoint, given the volume of COVID-19 cases and the chronicity and consequences of cognitive and psychiatric sequelae, there are likely to be substantial effects on health and social care systems.

Future Directions for Long COVID Recovery

Among the highest priority in supporting Long COVID recovery is addressing the stigma that individuals with Long COVID are facing. Perhaps because mental health disorders represent one aspect of the multifaceted nature of Long COVID, many have dismissed Long COVID as a psychosomatic condition with non-biological underpinnings. **This dismissal is contrary to scientific evidence and is exceptionally harmful for the patients and communities impacted.** Many individuals have been met with disbelief about their condition, leaving their

health needs entirely unaddressed. The mental health effects of this failure alone cannot be overstated. These challenges predominantly affect structural-level decision making and prevent adequate resources to be allocated in clinical settings.[100] Together with the ambiguity of its diagnostic criteria and a lack of appropriate treatment options, it is likely that the prevalence of Long COVID is drastically under-reported by patients and poorly recognized in clinical settings.[101] It is also worth noting that Long COVID bears a resemblance to several functional somatic syndromes (e.g., chronic fatigue syndrome, fibromyalgia) characterized by chronic symptoms of unclear etiology, which have also been historically associated with stigma.[102] As we move forward in the pandemic, national health systems have a responsibility to address stigma faced by Long COVID patients in order to ensure the best possible outcomes for their recovery.

Together with the ambiguity of its diagnostic criteria and a lack of appropriate treatment options, it is likely that the prevalence of Long COVID is drastically under-reported by patients and poorly recognized in clinical settings.

As Long COVID becomes increasingly recognized as a novel and potentially chronic health condition, healthcare systems will continue to face significant pressure from demands for services. From a clinical standpoint, managing patients with Long COVID will require a multidisciplinary effort, given the multiple organ systems often involved. Primary care physicians (PCPs) will likely be gatekeepers in this regard, and will be challenged with recognizing, documenting, managing ongoing symptoms, and directing patients to the appropriate line of care and treatment. In this light, PCPs should be made aware of the myriad of presentations of Long COVID and become familiar with the latest research. Routine assessment and screening for Long COVID symptoms, especially mental health and cognitive symptoms, would be particularly useful among those at greatest risk, such as those hospitalized for severe COVID-19. Importantly, PCPs and other specialists should also become aware of the local and virtual multidisciplinary resources to help patients manage symptoms of Long COVID. Finally, given potential cognitive limitations, it is imperative that all clinicians provide information in accessible formats, including resources for clinical trials and support groups in the community.

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Considering the high frequency of neurologic and psychiatric symptoms involved in Long COVID, neuropsychologists, behavioral neurologists, and psychiatrists have been especially in demand. However, the increased referral volume has already translated to substantially increased wait-times for appointments, further prolonging patients' options for recovery. Healthcare systems should consider integrating such specialists into primary care settings to promote more rapid clarification of diagnosis and treatment options for the debilitating cognitive and psychiatric symptoms experienced by some Long COVID patients. **Further, neuropsychologists and those administering neurocognitive testing should take special care in their selection of measures with adequate sensitivity and specificity, recognizing that the cognitive impairment present in this population may differ in severity than frequently seen in other populations (e.g., dementia).** Particular attention to cognitive reserve and patients' premorbid level of functioning will be critical in this regard.[103]

Given proven efficacy of cognitive rehabilitation (CR) for other clinical and healthy aging populations,[104,105] referrals for CR may also be prudent.

CR interventions have been shown to improve cognitive, emotional, and functional outcomes for other neurologic conditions, and studies using magnetic resonance imaging (MRI) have consistently shown structural and functional changes after CR in participants with acquired brain injuries (e.g., stroke, traumatic brain injury, chemotherapy-related CI).[106-112] CR is linked to the concept of neuroplasticity whereby, through practice, the brain can create new neural connections, or strengthen existing ones.[113] This leads to reinforcement of the trained cognitive capacity, and often to related abilities as well. Given accumulating evidence of COVID-19's potential to injure the brain,[114] together with objective data of post-COVID-19 cognitive and psychiatric sequelae across studies, it is likely that Long COVID patients could derive significant benefit from CR. However, there is not yet empirical data showing the benefits of CR in this population.

Healthcare systems should consider integrating such specialists into primary care settings to promote more rapid clarification of diagnosis and treatment options for the debilitating cognitive and psychiatric symptoms experienced by some Long COVID patients.

Dedicated Long COVID clinics have rapidly been established since the onset of the pandemic and are an excellent resource for comprehensive care. While many of these multidisciplinary clinics allow patients access to a variety of specialists in one place, others are more of a referral hub that helps triage patients with Long COVID and direct them to specialists within a particular healthcare system. The value of these dedicated clinics cannot be overstated; however, many of them lack the funding and resources to help their patients in a timely and efficient manner. For example, after being seen in a clinic, patients are often placed on long waitlists to be seen by other specialists. As such, integration of these specialists, such as neuropsychologists, who can address both the cognitive and psychiatric needs of these patients, would be extremely valuable. Furthermore, despite being embedded in major health systems and accepting all health insurance, many of the patients presenting to these clinics are affluent, privately insured individuals.[115] As such, health systems should consider providing more resources for community outreach and patient advocacy groups to improve access to care and inclusion of all individuals.

Long COVID can have highly variable impacts on patients' daily functioning. Fortunately, Long COVID is now considered a disability under the Americans with Disabilities Act (ADA), Section 504 of the Rehabilitation Act, and Section 1557 of the Affordable Care Act so long as it "substantially limits one or more major life activities,"[116] which can include a wide range of functional tasks such as caring for oneself, concentrating, sleeping, eating, and many others. Even if the functional impairment waxes and wanes, it can still be considered a disability. Under the ADA, individuals who qualify can be provided "reasonable modifications" at work, such as modified work hours, telecommunicating, phased returns, or a number of other accommodations.

> Health systems should consider providing more resources for community outreach and patient advocacy groups to improve access to care and inclusion of all individuals.

Unfortunately, many individuals with Long COVID have reported experiencing triggers and worsening of their symptoms upon returning to the stress of their jobs, despite accommodations. In cases where an individual is unable to perform essential job functions despite accommodation, they may qualify for long-term disability benefits if their symptoms have occurred for at least one year or longer. However, one of the significant challenges faced by individuals with Long COVID is that many of the Long COVID symptoms are self-reported (e.g., fatigue, difficulty concentrating, headaches, anxiety), which are often viewed unfavorably by long-term disability carriers and the Social Security Administration. Thus, treating clinicians will be instrumental in this regard, helping patients compile sufficient evidence of their condition and assisting disability carriers to differentiate legitimate claims from fraudulent ones.

With millions of individuals affected, cognitive and psychiatric sequelae pose significant public health challenges for patients' recovery. Healthcare systems will continue to require more financial resources to assess and treat Long COVID patients in a timely manner. More research will be needed to help clinicians streamline referral processes and make recommendations for evidence-based treatments.

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Methodological Limitations of Existing Studies and Goals for Future Research

The onset of the COVID-19 pandemic spurred a rapid acceleration of scientific endeavors, with approximately 4% of the world's research output devoted to COVID-19 in 2020 alone.[117] Not known at that time was that COVID-19 would extend into a prolonged post-acute syndrome for at least one third of survivors.[118-120] Despite the mountain of research on Long COVID since then, there are several outstanding research goals that need to be met in order to improve our understanding of the cognitive and psychiatric sequelae of Long COVID.

1. **Better operationalization of Long COVID through phenotyping.** The rapidly evolving research base and lack of non-standardized criteria has made prevalence estimates of Long COVID challenging. It has also impacted research on its etiology, treatment options, and diagnosis. The extant literature increasingly discusses the need to better operationalize Long COVID to allow for the development of appropriate diagnostic criteria. However, characterizing Long COVID as a single syndrome, as opposed to classifying individuals based on clinical presentation, may be hindering our understanding of the pathophysiology, prognosis, and consequently, effective treatment approaches. The range and severity of cognitive and psychiatric sequelae are varied and thus, an appreciation of this complexity across studies is critical. As we attempt to develop the nomenclature and operationalization of post-COVID-19 cognitive impairment, it would be prudent for researchers to avoid arbitrarily grouping all individuals within a single "Long COVID" box.

Long COVID is now considered a disability under the Americans with Disabilities Act (ADA), Section 504 of the Rehabilitation Act, and Section 1557 of the Affordable Care Act so long as it "substantially limits one or more major life activities."

The range and severity of cognitive and psychiatric sequelae are varied and thus, an appreciation of this complexity across studies is critical.

Several studies have already begun attempts to characterize phenotypes by clustering Long COVID symptoms. For example, one study utilizing a self-reported survey of 2,550 participants found that Long COVID symptoms mainly clustered in two groups: 1) a majority cluster, with 88.8% of the sample reporting fatigue, cardiopulmonary, and cognitive symptoms, and 2) a minority cluster (12%) with multi-organ symptoms and more severe functional impact associated with lower income and younger aged patients.[121] While informative, there are likely enormous differences in the pathophysiology and natural history of patients who were critically or severely acutely ill with COVID-19 versus those with mild or asymptomatic disease. Similarly, there are likely differential impacts on the CNS in older adults who are more susceptible to neurologic insults than younger adults. Thus, the underlying biology of cognitive and psychiatric symptoms may be entirely distinct, as well as the risk it confers for particular cognitive and behavioral trajectories (i.e., whereby some patients are more likely to improve, whereas others may remain impaired or continue declining).

Other phenotypes may also emerge in the process, such as individuals infected by differing COVID-19 variants, those with breakthrough infections following vaccination, and those with a history of other viral illnesses (e.g., EBV) or pre-existing autoimmune conditions.

2 **Inclusion of well-matched, non-infected control groups.** Pre-existing risk factors for cognitive decline are common in COVID-19 survivors,[122,123] making it challenging to determine the degree to which these and other pandemic-related factors may be contributing to post-COVID-19 cognitive symptoms.[122] Studies including well-matched non-COVID controls are needed[125,126] in order to help clarify whether COVID-19 is sufficient to cause and perpetuate cognitive and psychiatric symptoms. That is, there are substantial differences in cognitive functioning and mental health of those *infected* by SARS-CoV-2 in comparison to those *affected* by the pandemic, and thus non-infected control groups will be critical to our understanding of the biological underpinnings of Long COVID cognitive and psychiatric symptoms.

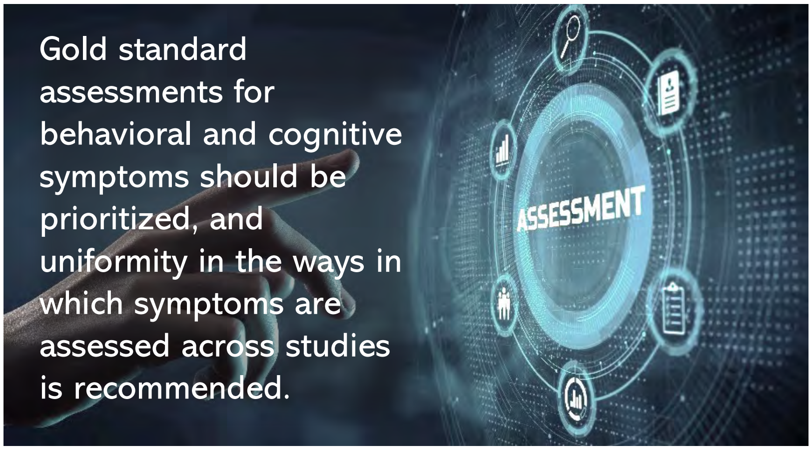
Researchers studying the cognitive and psychiatric sequelae of Long COVID should attempt to further delineate subtypes by studying symptoms and trajectories of particular groups stratified by

- ✓ COVID-19 severity
- ✓ Age
- ✓ Pre-existing cognitive and/or mental health disorders
- ✓ Family history of dementia or mental health disorders which predispose patients to have cognitive impairment or mental health sequelae.

3 **More rigorous assessment of cognitive and psychiatric symptoms.** Robust collection of cognitive and mental health data has been hindered by COVID-19's transmissibility and social restrictions of the pandemic. Most studies have resorted to suboptimal assessments, including remote (e.g., online or telephonic) administration of cognitive measures,[127,128] self-reported surveys of cognitive dysfunction and mental health disorder,[129] and utilization of brief dementia screeners (e.g., the Montreal Cognitive Assessment),[130-132] which are not sensitive for milder cognitive impairment.[133] Similarly, brief telephonic surveillance reports have been widely used to screen for post-COVID-19 psychiatric symptoms, which are often unreliable.[134,135] Further, there is considerable variability across studies in the screening tools used and their respective cutoffs. Gold standard

assessments for behavioral and cognitive symptoms should be prioritized, and uniformity in the ways in which symptoms are assessed across studies is recommended.

4. **Assessment across the spectrum of COVID-19 severity.** Studies on post-COVID-19 cognitive impairment have largely focused on hospitalized patients with severe disease.[136-139] However, these studies are not representative, as the majority of COVID-19 survivors have mild to moderate disease and do not require hospitalization. This is particularly true for the most recent COVID-19 survivors infected with the Omicron variant or for vaccinated individuals with breakthrough infections. More recent investigations have shifted to studying those with mild COVID-19, but follow-up times have been variable, making it difficult to determine a particular trajectory.



Researchers should consider studying individuals across the spectrum of disease severity, using recommended guidelines[140] in order to appropriately characterize the prevalence and trajectories of cognitive and psychiatric sequelae across groups.

5. **Improve sampling and inclusion of racial and ethnic minority groups.** Several studies have inherent sample or selection biases, whereby only participants presenting with specific Long COVID concerns or attending specialized post-COVID clinics are included, rather than including a larger sample of all COVID-19 survivors. This is particularly problematic given that the majority of participants with access to specialized post-COVID clinics tend to be affluent and privately insured. As such, despite the disproportionate impact of COVID-19 on racial and ethnic minorities,[141] these populations have been underrepresented in Long COVID studies. Inclusion of minoritized groups will be crucial moving forward in order to improve generalizability of results. To that end, researchers should consider establishing community outreach and patient advocacy programs in order to increase awareness of Long COVID, reduce stigma of cognitive and psychiatric sequelae, and engage community members in Long COVID research. It would also be prudent to directly engage patients in the description of their Long COVID symptoms.

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6. **Other recommendations.** Other epidemiological limitations have also been highlighted as methodological concerns in current research.[142] Small sample sizes plague existing studies, resulting in low power, limited

external validity, and an inability to properly control for potential confounders.[143,144] For example, it is well known that psychological morbidity, psychosocial stressors, and sociocultural factors are bidirectionally associated with cognitive impairment, and thus, all of these factors should be accounted for in future studies. **There is also a need to explore interactions of social, structural, and systemic inequalities, and other medical comorbidities, with risk of mental health and cognitive sequelae.** More rigorous and

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standardized criteria for defining COVID-19 status (e.g., serology confirmed vs. self-reported) and COVID-19 disease severity is also needed.

To some degree, the limitations mentioned above were expected early in the pandemic, given its rapid onset and associated practical and safety limitations. However, over two years into the pandemic, it is both feasible and necessary for researchers to change their approach in order to facilitate our understanding of the prevalence, risk factors, and biological bases of Long COVID-related cognitive and psychiatric sequelae, in order to provide appropriate management and care to patients.

Summary and Conclusions

The COVID-19 pandemic has had profoundly adverse impacts on cognitive and mental health at the population level. While significant advances have been made, scaling up proven cognitive and mental health strategies and interventions to meet the ever-growing needs of patients with Long COVID continues to be a challenge. Large gaps remain between the number of people who need care for Long COVID cognitive and psychiatric sequelae and those who receive it. To that end, greater allocation of healthcare resources is needed to adequately support and provide interdisciplinary care to patients with Long COVID, with particular attention to health equity and equal access to care for all populations.

As we develop best practices for treatment and management of patients with Long COVID, we must also promote a reduction in the stigma associated with the condition. While recognizing the psychological aspects of Long COVID is critical, an over-emphasis can be harmful and present major barriers to healthcare seeking, increased social marginalization and distrust in medicine, and distortion of public perceptions of risk.[145] A reduction in Long COVID stigma will allow for greater mobilization of resources to refine Long COVID definitions and help increase our understanding of its pathophysiology.

Finally, development of easily accessible treatment approaches for cognitive and psychiatric sequelae is also in great need. Despite the clear pattern of brain changes associated with Long COVID, the brain's plasticity, or capacity for a degree of structural and functional recovery, is believed to exist across all individuals, regardless of age or health status.[146] Thus, it is of great scientific and clinical relevance to continue to improve our understanding of Long COVID due to the possible reversibility, opportunities for prevention, intervention, and mitigation of long-term consequences.

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